Indian J Lepr 2018, 90 : 173-175

http://www.ijl.org.in

Opinion Article

Grey areas in tuberculosis research: need to pay more attention

Babban Jee[1]

Received : 16.01.2018 Accepted : 31.03.2018

Tuberculosis research spanning over a century period, has led to several important breakthroughs. These discoveries have helped in developing microbiological and molecular methods for diagnosis. Efforts on drug discovery have provided several effective anti-TB drugs that have made the treatment highly effective. However, adaptation of *Mycobacterium tuberculosis* and resultant drug resistance/unresponsiveness has created a challenging situation. Further, capacity of this pathogen to lie dormant in the body for years together results in a big pool of hidden disease and potential reservoir of infection. While, there is gradually improving understanding of mechanisms of dormancy, it is still patchy and not enough. Focusing on these areas will prepare us better to tackle the disease in the long run. It will be highly desirable to concentrate the scientific efforts on these grey areas of tuberculosis research.

Keywords : Grey Areas, Tuberculosis Research, Dormancy, Resistance, Unresponsiveness

Tuberculosis still continues to be a major health issue of the world. It is caused by a slow growing, non-motile, non-spore forming and acid-fast pathogen *Mycobacterium tuberculosis* (MTB). In 2016, about 1.3 million people died from tuberculosis and approximately 6.3 million people got new infections of MTB. The emergence of HIV/AIDS resulted in rise of the toll of TB associated deaths and morbidities. It was estimated that in 2016, approximately 374000 HIV - positive people have lost their lives due to tuberculosis. By virtue of this worldwide spread and prevalence, TB continues to be a leading cause of death from a single infectious agent by replacing HIV/AIDS from top seat during the last 5 years (WHO 2017).

The pathogenesis of MTB starts with entry of this organism into human mainly through inhalation of infectious droplet nuclei containing MTB. After inhalation, MTB reaches to deep of respiratory tract where it is taken up by professional phagocytic cells (e.g. macrophages) thorough various kinds of surface receptors including opsonizing receptors, scavenger receptors, C-type lectin receptors and toll like receptors (TLRs) (Pieters 2001). The interaction of MTB and macrophages leads to activation of innate mechanism resulting into generation of wide spectrum of immune responses to contain the infection. The development of phagolysosomes and granuloma are some major events of the host immune system. Eventually, interplay of innate

[1] Babban Jee, PhD, Scientist - C, Department of Health Research, Ministry of Health and Family Welfare, Government of India, New Delhi, India

Correspondence : Dr. Babban Jee, **email :** babban.jee@gov.in

and acquired immune branches of host produces a range of antimicrobial products that act against intracellular MTB to kill it (Weiss & Schaible 2015).

To treat the disease, various synthetic drugs were developed over the years. Some of them are now part of standard anti-tuberculosis therapy (ATT) which includes ethambutol, isoniazid, pyrazinamide, rifampicin and streptomycin. Initially these drugs had raised hope for world but later on their injudicious and unguided application resulted in emergence of various drug resistant forms (e.g. MDR, XDR and TDR) of MTB (Palomino and Martin 2014). Currently, entire world is fighting against these drug-nonresponsive phenotypes of MTB and thinking of devising new strategy(ies). For effective control of TB, WHO recommended directly observed treatment short course (DOTS) in early 1990s. The introduction of DOTS in TB treatment programme has resulted in control of disease all over the world, however, due to various biological and social reasons resistance has also been on the increase. Since MTB has excellent capability to sense the external stimuli and adapt accordingly, so a single component based strategy is largely unsuccessful. So, it would be a wisely step, if we develop more smart/advanced strategy(ies) than existing ones. Furthermore, development of drug(s) from plant/natural products may be helpful in resolving the issues regarding intolerable side effects of synthetic drugs.

A number of methods were developed in past to detect the pathogen in patient samples. Of these, culture of tubercle bacilli is still gold standard method of diagnosis, however, this is not sensitive in paucibacillary forms of disease, needs long time and extra facility to give its result. After the whole genome sequencing of MTB by Cole and his colleagues in 1998 (Cole et al 1998), the world of tuberculosis research witnessed a revolutionary change. The development of gene specific diagnostic methods has been impacted by that breakthrough work. Now a day, Xpert® MTB/RIF assay (Cepheid, USA) is a more accurate and rapid molecular diagnostic method in practice, however, its higher cost and specific requirement for its implementation hindering it from mass access in low-economic countries where basic health facilities are largely unavailable. Thus, there is time to re-visit the requirement of less developed and economically poor countries so that a more appropriate, cost-effective and affordable method could be developed.

Besides, there are many grey areas where much work is required. Latent tuberculosis is such an area which is still less understood. Clinically, latent tuberculosis represents the state of MTB infection in which this pathogen becomes quiescent by arresting its most of metabolic activities and remaining alive in host body for a longer period, without producing any clinical symptoms or sign of TB. When host immunity weakens, then this quiescent form of tubercle bacilli reactivates and causes active disease. Hence, latent tuberculosis is treated as a reservoir of possible MTB infections. Since, the optimal time for reactivation of non-replicating but metabolically active dormant MTB is not known, so, it is entirely impossible to predict the time of resurgence of active tuberculosis during lifetime of an infected human. In this context, there is dire need to systematically study all events of latent tuberculosis and accurately identify the latent form of MTB in general population. For doing this, mass level screening would be required. There is also a requirement to study various attributes of a latent form of MTB and factors that help it in its survival. Amongst various factors known, a small heat shock protein 16.3 (sHSP16.3) is supposed to be crucial for the survival of MTB. Experimental evidences suggest that this protein acts as a

facilitator of dormancy of MTB and protects MTB by preventing its building blocks (i.e. protein) from denaturation during host's attack (Jee et al 2008). Recently, efforts have been made to modulate the expression of *hspX* gene encoding this protein by a combination of cytokines and to develop inhibitors of sHSP16.3 (Jee et al 2017a, b), but these attempts are not enough to decipher the biology, mode of action and importance of this crucial protein in tuberculosis. A lot of work in mission mode is needed.

References

1. Cole ST, Brosch R, Parkhill J et al (1998). Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature.* **393**: 537-544.
2. Jee B, Katoch VM, Awasthi SK (2008). Dissection of relationship between small heat shock proteins and mycobacterial diseases. *Indian J Lepr.* 80: 231-245.
3. Jee B, Kumar S, Yadav R, Singh Y, Kumar A, Sharma N (2017b). Ursolic acid and carvacrol may be potential inhibitors of dormancy protein small heat shock protein 16.3 of *Mycobacterium tuberculosis. J Biomol Struct Dyn.* 1-10.
4. Jee B, Sharma P, Katoch K, Joshi B, Awasthi SK (2017a). IL-10 down-regulates the expression of survival associated gene *hspX* of *Mycobacterium tuberculosis* in murine macrophage. *Braz J Infect Dis.* **21**: 386-390.
5. Palomino JC and Martin A (2014). Drug resistance mechanisms in *Mycobacterium tuberculosis. Antibiotics (Basel).* **3**: 317-340.
6. Pieters J (2001). Entry and survival of pathogenic mycobacteria in macrophages. *Microbes Infect.* **3**: 249-255.
7. Weiss G and Schaible UE (2015). Macrophage defense mechanisms against intracellular bacteria. *Immunol Rev.* **264**: 182-203.
8. World Health Organization (2017). Global tuberculosis report. WHO, Geneva, Switzerland.

How to cite this article : Babban Jee (2018). Grey areas in tuberculosis research: need to pay more attention. *Indian J Lepr.* **90** : 173-175.